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Paradigm shift in hypomagnesemia: a prospective observational study of ionized magnesium in the ICU

Jelle P. Zwart^{1*} , Mike Zwartkruis², Marcel M. G. J. van Borren³, Jan van Vliet² and Anna P. Bech¹

Dear Editor,

Hypomagnesemia is frequently encountered in patients admitted to the intensive care unit (ICU) [1, 2]. Several reports have shown that hypomagnesemia on the ICU is associated with critical illness and ICU outcome, but it is unclear whether this concerns a causal relation [1, 3]. While total magnesium is often used in routine care, ionized magnesium appears to be the best possible test [2]. Understanding the underlying mechanism is necessary for moving forward in treatment regimens.

We therefore performed a prospective study in an ICU of a teaching hospital in the Netherlands. This ICU admits general medical and surgical patients, except acute neurosurgery and cardiothoracic surgery patients. All patients admitted to the ICU receive standard nutritional care, starting on day 1 and with a preference for enteral nutrition. Patients were screened each day for the first 7 days on the ICU for hypomagnesemia (ionized serum magnesium < 0.45 mmol/L). Patients with low serum ionized magnesium were included for further screening. We continued the study until a total of 10 patients were included. Magnesium supplementation was given according to the attending clinicians preferences.

The incidence of ionized hypomagnesemia in our study population was 15% (15/99 patients). The incidence of hypermagnesemia (ionized magnesium > 0.60 mmol/l) was 52% (52/99). All patients who developed ionized

hypomagnesemia showed this within 24 h of admittance to the ICU, except one. In all patients magnesium levels rose during their stay on the ICU, even when no supplementation was given (Fig. 1). In general, ionized and total magnesium levels correlated well ($R^2 = 0.92$, $p < 0.01$) but the amount of mislabeled hypomagnesemia based on total magnesium was relatively high: in 13 out of 29 low total magnesium levels, there was a concomitant normal ionized magnesium (= 45%). Levels of albumin and pH were not different in these patients compared to the overall group. The amount of mislabeled normomagnesemia based on total magnesium was low: there was only one instance of a low ionized magnesium with a normal total magnesium, in contrast to 16 measurements of low ionized magnesium with a concomitant low total magnesium (= 6%).

Patients with an ionized hypomagnesemia all showed low concentrations of urine magnesium. The mean amount of magnesium in the 24 h urine samples collected on the first day after diagnosis was 1.2 mmol. Compared to the median supplementation of over 2 g of MgSO₄ (~ 8 mmol of Mg) in the same period, this is also low.

PTH levels were elevated in these patients with mean levels of 20 pmol/L and calcitriol was decreased, mean 36 pmol/L.

Our study shows that a low total magnesium does not necessarily implicate the presence of true ionized

*Correspondence:

Jelle P. Zwart

jelle@zwart.nu

¹Department of Internal Medicine, Rijnstate Hospital, Arnhem, the Netherlands

²Department of Intensive Care, Rijnstate Hospital, Arnhem, the Netherlands

³Department of Clinical Chemistry, Hematology and Immunology, Rijnstate Hospital, Arnhem, the Netherlands



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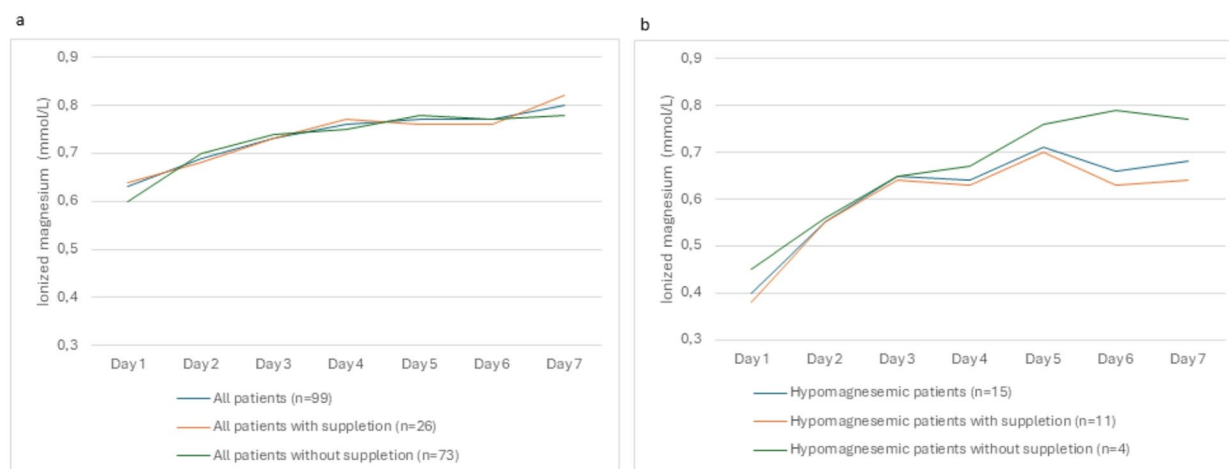


Fig. 1 (a) mean ionized magnesium levels in time. (b) mean ionized magnesium levels for subset with ionized hypomagnesemia

hypomagnesemia, but a normal total magnesium level typically rules out ionized hypomagnesemia. This is in contrast with the only other general ICU-study that we know of that measured ionized magnesium [2]. This raises pertinent questions regarding the clinical significance of total magnesium measurements on the ICU, especially considering the prevalent practice of magnesium supplementation and the ongoing uncertainty surrounding the clinical relevance and etiology of hypomagnesemia.

The number of patients with hypermagnesemia was also remarkably high. Possible explanations could be that the upper limit of normal may be unsuitable for ICU patients, or it could be caused by cellular shift of magnesium.

Our findings shed light on the early onset and fast recovery of ionized hypomagnesemia, even without supplementation. This is the case for both ionized and total hypomagnesemia, which means that this effect cannot be caused by a significant redistribution of magnesium in plasma. We also showed that ICU induced hypomagnesemia is not caused by increased urinary magnesium loss. As magnesium changed so rapidly, it is also not likely to be caused by exchange in the bone surface pool, which takes several days [4]. Together, these results suggest that ICU induced hypomagnesemia is based on a cellular shift of magnesium and not on a true total body magnesium deficit. What exactly causes this cellular magnesium shift is not clear yet. What we do know is that cellular magnesium transport is influenced by different hormones such as catecholamines and factors that influence cellular ATP content and production. This transport is fast, and cells can extrude up to 15% of their total cellular magnesium content within a few minutes after stimulation [5].

Altogether, we hypothesize that in patients who develop hypomagnesemia (and hypermagnesemia?) shortly after ICU admission, magnesium shifts into or

out of the cell under the influence of factors involved with critical illness. Hypomagnesemia may thus only be a marker of ICU induced stress. This novel perspective raises an important question regarding the appropriateness of magnesium supplementation in this population and warrants further examination, for instance through prospective interventional studies.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s13054-025-05630-1>.

Supplementary Material 1.

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Author contributions

JZ collected and analysed the data and wrote the manuscript. MZ collected the data and reviewed the manuscript. MB was responsible for laboratory testing and reviewed the manuscript. JV was responsible for data collection oversight and reviewed the manuscript. AB was responsible for study oversight and wrote and reviewed the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the guidelines of the Declaration of Helsinki and according to the regulations of the local medical ethical committee. Permission to start with the study 'Hypomagnesaemia in the ICU' was obtained on 02-04-2021 from the local committee in our hospital in Arnhem, the Netherlands with reference number 21.060/2019–1472. All participants or family members gave written informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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